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CONTRACTING ORGANIZATION: Howard University
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14. ABSTRACT

Macrophage function can be regulated by breast cancer cells to sustain an inflammatory microenvironment that promotes cancer cell proliferation and survival. MCF-7 cells suppress IL-10 expression by co-cultured macrophages. Activated and resting THP-1 macrophages were able to induce *SNAIL* expression in MCF-7 cells. SNAIL has been implicated in the epithelial-mesenchymal transition which precedes metastasis. These observations suggest that tumor-associated macrophages may promote progression-related gene expression at discrete steps in the progression cascade. Both Faslodex™ and tamoxifen were effective in up-regulating pigment epithelium-derived factor, a potent anti-angiogenic cytokine, and in down-regulating *SNAIL* in MCF-7 cells.

15. SUBJECT TERMS
Tamoxifen, Faslodex™ metastasis, apoptosis, MCF-7, MDA-MD-231, macrophages

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INTRODUCTION

Three months ago, I applied for, and received, a no-cost extension for one year to complete the remaining tasks on the project. Gay S. Morris, who worked on this project as a graduate student is now completing the first year of a postdoctoral fellowship in breast cancer in the Laboratory of Dr. Kent C. Osborne at the Breast Center, Baylor College of Medicine. Because funding for the post-doctoral fellow expired in June, 2005, Dr. Zhe Jin applied for another position and was successful. He is currently in cancer research in the Department of Medicine at the University of Maryland. A new graduate student, Ms Tracy Davis and two undergraduate honors students, Denise Weathersby and Giselle Burnett, have joined the laboratory and are currently assisting in the completion of the project. All of them wish to pursue careers in breast cancer research.

BODY

In the past year, we have been able to present posters at the 44th Annual Meeting of the American Association for Cell Biology (December 4 – 8, 2004) and at the Era of Hope Meeting in Philadelphia (June 8 – 11, 2005). The task to be completed is 2(c), Western blotting, ELISA for cytokines, RT-PCR (Months 24 - 36).

STATEMENT OF WORK

Tamoxifen and tumor-associated macrophages

Task 1. Determine the effect of *in vitro* co-culture on gene expression in BC cells and THP-1-macrophages (Months 1 - 18):

(a) Recruitment of postdoctoral fellow (Months 1 - 2)
(b) Grow cells, set up co-cultures of BC and THP-1 macrophages (Months 1 - 7)
(c) Isolate mRNA for gene expression array analysis, Months 4 - 12
(d) Standardize and calibrate gene expression arrays for proliferation-related gene expression in BC cells co-cultured with THP-1 macrophages (Months 11 - 18)

Task 2. Studies on effects of anti-inflammatory and macrophage-modulating compounds on macrophage and BC gene expression (Months 16 - 36):

(a) Co-culture of cells for studies on the effects of anti-inflammatory agents (Months 16 - 30)
(b) Isolation of mRNA for gene RT-PCR, and gene expression arrays for Task 2 (Months 17-30)
(c) Western blotting, ELISA for cytokines, RT-PCR (Months 24 - 36)

In the past year, we have looked at the ability of resting and lipopolysaccharide-activated TPH-1 macrophages to regulate tumor promotion-related gene expression in MCF-7 cells and MDA-MB-231 cells. Our findings show that macrophage function can be regulated by breast cancer cells. MCF-7 cells can suppress IL-10 expression in co-cultured macrophages. Because IL-10 is a potent anti-inflammatory cytokine suppression of macrophage IL-10 production by breast cancer cells may be a mechanism by which tumors sustain an inflammatory microenvironment. Our results confirm previous findings that tamoxifen down-regulates VEGF (1). However, we found that tamoxifen can up-regulate PEDF pigment epithelium-derived factor (PEDF), the most

potent angiogenesis inhibitor identified to date. This finding has not been previously reported in the literature. PEDF antagonizes VEGF signaling via a JNK-mediated pathway that inhibits the transcription factor NFAT (2). These findings provide new insights into the chemopreventive and chemotherapeutic effects of tamoxifen.

We observed that MDA-MB-231 cells are less firmly attached to the substratum and possess a more "motile" morphology than MCF-7 cells. Because inflammatory cytokines secreted by macrophages may act at different stages in tumor progression, we looked for differences in the expression of candidate genes identified in our gene arrays that may be expressed during the epithelial-mesenchymal transition (EMT), and that may also be susceptible to regulation by inflammation. We compared the expression of the transcription factor SNAIL (3) by RT-PCR and Western blotting to determine whether its expression is regulated by macrophages. Our results show that the levels of *SNAIL* expression in MDA-MB-231 cells are not affected by culture with macrophages. However, when MCF-7 cells are co-cultured with resting THP-1 macrophages, *SNAIL* expression is induced. When LPS-activated macrophages were used, the levels of SNAIL expression in MCF-7 were even higher. These observations suggest that macrophages may promote tumor progression by acting at discrete stages in in the progression cascade.

KEY RESEARCH ACCOMPLISHMENTS

We have discovered that:

- MCF-7 cells can suppress IL-10 expression in co-cultured macrophages.
- Tamoxifen down-regulates VEGF in both MCF-7 and MDA-MB-231 cells.
- Tamoxifen can up-regulate PEDF pigment epithelium-derived factor (PEDF), the most potent angiogenesis inhibitor identified to date.
- LPS-activated macrophages induce SNAIL expression in MCF-7 cells
- Both Tamoxifen and Faslodex™ can down-regulate *SNAIL* expression in breast cancer cells.

REPORTABLE OUTCOMES

"Reciprocal Regulation of Angiogenesis-related Gene Expression in Co-cultured MCF-7 Breast Cancer Cells and THP-1-derived Macrophages." Poster presented at the 44th Annual Meeting of the American Society for Cell Biology, Washington, DC, December 4 – 8, 2004. (Abstract in APPENDICES)

"Macrophages Protect Breast Cancer Cells from Tamoxifen Killing" Poster presented at the 2005 **Era of Hope** Meeting, Philadelphia, PA. Abstract in APPENDICES

Dr. Zhe Jin, a post-doctoral trainee supported by this project from January 2004 to May 2005, has been employed in the Department of Surgery, University of Maryland School of Medicine.

CONCLUSIONS

Our work provides evidence that macrophages may contribute to tumor progression by regulating specific gene expression at discrete stages in the promotion cascade. The suppressive effects of tamoxifen and Faslodex on metastasis-related gene expression may be an important aspect of their chemotherapeutic and chemopreventive properties.

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APPENDICES

Abstract L186, 44th Annual Meeting, American Society for Cell Biology, Washington, DC, Dec. 4 – 8, 2004

Tamoxifen up-regulates pigment epithelium-derived factor in MCF-7 breast cancer cells under normoxia and hypoxia. **Zhe Jin**, Gay S. Morris, and Theodore A. Bremner, Department of Biology, and Howard University Cancer Center, Howard University, Washington, DC 20059 and 20060.

It is now generally accepted that stromal cells play important roles in tumor progression by secreting cytokines and growth factors that promote angiogenesis, invasion, and metastasis. Because the reciprocal interactions between cancer cells and stromal cells may comprise a class of emergent targets for therapeutic intervention, a fuller understanding of the effects of anticancer drugs on stromal cells within the context of the tumor microenvironment is warranted. We undertook to study the effects of tamoxifen on the transcriptional profiles of both MCF-7 breast cancer cells and THP-1-derived macrophages co-cultured in Transwell plates to simulate a tumor environment. We used a combination of pathway-focused gene arrays, RT-PCR and Western blotting to determine how each cell type influences the regulation of 96 angiogenesis-related genes in the other, and to assess the effects of sub-lethal concentrations of tamoxifen on these gene-regulatory interactions. We found that THP-1 macrophages in isolation expressed both vascular endothelial growth factor (*VEGF*), a major activator of pathological angiogenesis, and pigment epithelium-derived factor (*PEDF*), a potent inhibitor of angiogenesis. However, when co-cultured with THP-1 macrophages, *VEGF* expression was essentially unaffected, whereas *PEDF* expression was dramatically down-regulated. In addition, tamoxifen potently up-regulated PEDF protein, although PEDF mRNA levels were essentially unchanged, consistent with earlier reports that *PEDF* expression is post-transcriptionally regulated. We also found that co-culture with MCF-7 up-regulated the inflammatory cytokine IL-1β in THP-1 macrophages, and inhibited the expression of the anti-inflammatory IL-10 by the macrophages. These observations are consistent with the view that tumor cells require an inflammatory milieu and suggest further that they may regulate the behavior of stromal macrophages to maintain an inflammatory microenvironment.

Tumor-associated macrophages have been implicated in several aspects of tumor progression, including angiogenesis, invasion, and metastasis. Because the macrophage phenotype is extremely plastic and determined largely by its tissue environment, regulatory loops between tumor cells and macrophages may constitute a class of emergent targets for therapeutic intervention. A fuller understanding of these interactions and the effects of anti-cancer drugs on their regulation and functionality is, therefore, warranted. We studied the effects of tamoxifen on the reciprocal regulation of gene expression caused by paracrine interactions between MCF-7 breast cancer cells and THP-1-derived macrophages co-cultured in Transwell plates.

Abstract P52, Era of Hope Meeting, Philadelphia, PA, June 8 – 11, 2005

MACROPHAGES PROTECT BREAST CANCER CELLS FROM TAMOXIFEN KILLING **Theodore A. Bremner, Zhe Jin, and Gay S. Morris,** Department of Biology, and Cancer Center, Howard University, Washington, DC 20059 **tbremner@howard.edu**

Tamoxifen (TMX) is widely used for the treatment of estrogen receptor (ER)-α-positive breast cancers, but its effectiveness is limited by the eventual development of cellular resistance. Abundant evidence suggests that stromal cells, including macrophages, promote tumor progression. Therefore, the genetic events that underlie progression and resistance may occur in tumor cells and stromal cells. TMX binds to and alters ER-α function, but up-regulates many estrogen-responsive genes. ER-α signaling is required to suppress metastasis-associated genes, and loss of ER-α function in tumors can trigger epigenetic silencing of ER-α target genes leading to a more aggressive phenotype. By antagonizing ER-α, TMX may inhibit growth of breast cancer cells while promoting epigenetic changes that pre-adapt them to later stages of progression.

MCF-7 breast cancer cells and THP-1-derived macrophages (Mϕs) were co-cultured in Transwell™ plates under normoxia and hypoxia and gene arrays, RT-PCR, and Western blotting were used to detect changes in inflammation- and angiogenesis-related gene expression. We hypothesized that (1) Mϕs, may secrete factors that promote tumor growth and drug resistance, and (2) tamoxifen (TMX) may stimulate Mϕ production of inflammatory, angiogenic, or metastatic factors despite its ability to inhibit tumor growth. Co-cultures were treated with varying concentrations of TMX (0 – 15 μM) for 3 d under normoxia or hypoxia. Under both conditions, MCF-7 cells proliferated more rapidly when co-cultured with Mϕs, and were more resistant to TMX-induced apoptosis. This protection was abrogated by aspirin (1 mM). TMX (10 μM) down-regulated vascular endothelial growth factor (*VEGF*), but up-regulated the hypoxia-inducible factor-1α (*HIF-1α*) in MCF-7 cells under hypoxia. Mϕs induced the expression of interleukin-8 (*IL-8*), and the TGF-β receptors-1, 2, and 3 (*TβRs, 1, 2, 3*) among others, in MCF-7 cells. MCF-7 cells dramatically up-regulated several inflammatory cytokine genes in Mϕs, including *IL-1β* and *TGFβ1*. In contrast, when MCF-7 cells were pre-treated with TMX, *IL1β* expression was decreased, *TGFβ1* expression was lost, and *TGFβ3* and stromal-derived factor-1α (*SDF-1α*) were induced. Macrophage migration inhibitory factor (*MIF*) was expressed constitutively by Mϕs and TMX did not affect its expression. Co-culture with MCF-7 decreased *MIF* expression in Mϕs. However, when Mϕs were co-cultured with TMX-treated MCF-7, there was a dramatic up-regulation of *MIF*. TMX down-regulated *MIF* in MCF-7 cells except when Mϕs were present. MIF can suppress apoptosis in tumor cells by interfering with p53 function. MCF-7 cells dramatically down-regulated *IL-10* expression in Mϕs, suggesting that tumor cells can elicit responses from macrophages to maintain an inflammatory environment. TMX up-regulated *PEDF* (pigment epithelium derived factor) in MCF-7 cells and down-regulated *VEGF*.

Our results confirm that breast cancer cells can elicit transcriptional responses in Mϕs, and that TMX can alter paracrine interactions between them. Tumor-stroma interactions represent an emergent class of therapeutic targets, a fuller understanding of which will permit the design of combination therapies that maintain TMX effectiveness while suppressing resistance. The U.S. Army Medical Research and Materiel Command under DAMD17-02-1-0408 supported this work.

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CITIZENSHIP: United States

EDUCATION: Ph.D., (zoology, biochemical genetics, minor in microbiology) Howard University, 1972
M.S., (zoology) Howard University, 1970
B.S., (zoology) Howard University, Washington, DC, 1968

EXPERIENCE

7/1/92 to present:	**Associate professor, Department of Biology, Howard University.**
8/1/94-6/30/03	**Graduate associate professor**, Graduate School of Arts and Sciences, Howard University (94-97; 97-00; 00-03).
2/4/02-1/31/04	**Guest Researcher**, Cancer Genetics Branch, National Human Genome Research Institute, NIH; Laboratory of Dr. Paul Meltzer, Head, Section on Molecular Genetics. (301) 594-5283.
5/16/97-5/15/00	**Adjunct associate professor of molecular biology**, Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University, Providence, RI.
8/15/96-05/15/97	**Howard Hughes Visiting Associate Professor of Molecular Biology (Research)**, Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI.
Summer 1994:	**Adjunct associate professor**, Department of Genetics, College of Medicine, University of Illinois at Chicago.
1990 to present	**Member, Basic Sciences Faculty**, Howard University Cancer Center.
1987-1990	**Director of the Honors Program**, College of Liberal Arts (now College of Arts and Sciences), Howard University.
1985-1992:	**Associate professor**, Department of Zoology, Howard University.
1986-1988:	**Graduate associate professor**, Graduate School of Arts and Sciences,
1981-1985:	**Lecturer**, Department of Zoology, Howard University.
1979-1980:	**Assistant professor**, Department of Biology, Texas Southern University, Houston, TX. Taught General Biology (team-taught course), Genetics, Developmental Biology, and Biochemistry.
1978-1979:	**Lecturer**, Department of Zoology, Howard University. Participated in team-taught course in molecular biology for senior undergraduates and graduate students
1972-1978:	**Assistant professor**, Department of Botany, Howard University.

1976: **Macy Scholar**, Marine Biological Laboratory, Woods Hole, MA. Graduate course in embryology (molecular biology and biochemistry of development); did post-course research on the expression of differentiated function in isolated blastomeres of *Arbacia punctulata*. (June - September).

1974: **Guest worker**, Laboratory of Chemical Biology, National Institute of Arthritis, Metabolic and Digestive Diseases, NIH, Bethesda, MD. Worked in the laboratory of Dr. Christian B. Anfinsen, Nobel Laureate, on the purification of aminoacyl tRNA synthetases.

1973: **Volunteer botanist**, USDA Laboratory of Forestry Sciences, Durham, NH. Studied chemical and biological processes in discoloration and decay of northern hardwoods (with Dr. Alex Shigo, plant pathologist).

1973-1975: **Personal contractor**, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, NIH. Biochemical analysis of genetic markers in the mouse.

1972-1973: Collaborative research with Dr. Wallace P. Rowe, Chief, Laboratory of ViralDiseases (LVD), NIAID, and Dr. Janet Hartley, on the mapping of the murine leukemia viral genome in AKR mice.

1971-1972: **Terminal (Ph.D.) Fellow**, Howard University.

1970: **Lucy Moten Fellow**. Visiting researcher, Instituto de Biociencias, Universidade de São Paulo, São Paulo, Brasil. Worked in the laboratory of Professor Renato Basile on the cytogenetics of *Rhyncosciara angelae* (June - September).

RESEARCH INTERESTS

Monocyte/macrophage/dendritic cell differentiation, and myeloid leukemia.
Macrophage modulation of breast cancer cell susceptibility to cytokine- and drug-induced apoptosis.

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American Association for Cancer Research
American Association for the Advancement of Science
American Society for Cell Biology
Society for Leukocyte Biology

PROFESSIONAL DEVELOPMENT:

1981 **Laboratory Use of Radioactive Materials** (Chemistry 231). Foundation for Advanced Education in the Sciences, National Institutes of Health, Bethesda, MD. Lecture/laboratory course conducted by John Goble.

1982 **Radiation Safety.** Howard University School of Engineering, Lecture Laboratory course conducted by Prof. Ferguson.

1983 **Monoclonal Antibody Production.** Center for Advanced Training in Cell and

Molecular Biology, Catholic University of America. Lecture laboratory workshop, Boston, 1983.

1989 **Clinical and Research applications of Human Tissues and Cells.** Two-day seminar sponsored by American Association of Tissue Banks, American Council on Transplantation, and the Tissue Culture Association (NCAB/TCA) Stouffer's Concourse Hotel, Arlington, VA, March 6 - 7, 1989.

1990 **Ascorbic Acid: Biological Functions and Relation to Cancer.** Lister Hill Auditorium, NIH, September 10 - 12, 1990.

1990 **Recombinant DNA Methodology**. Exon-Intron, Inc., Columbia, MD. Conducted by Drs. Robert E. Farrell and Gregory S. Leppert, November 5 - 9, 1990.

1991 **Oxygen Free Radicals.** Symposium held at the National Institutes of Health (Jack Masur Auditorium, Bldg., 10), Bethesda, Md.

1993 **Workshop on Cell Cycle Progression, Aging, and Cell Death.** Sponsored by the Division of Research Grants, Molecular Cytology Study Section. Scheduled for Builing 60, Room 162, The Cloister, 1 Cloister Court, NIH. Held at The Holiday Inn, Bethesda, MD (due to very high registration).

1994 **4th Annual Symposium in Molecular and Cell Biology**. Molecular and Cell Biology Program, University of Maryland at Baltimore, Medical School Teaching Faculty Auditorium, 10 S. Pine St., Baltimore, MD, Wednesday 4/27/1994.

1995 **International Centers for Tropical Disease Research, Fourth Annual Meeting**. Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), NIH. Lister Hill Auditorium, Bethesda, MD April 26-28, 1995.

1998 **Leadership Through Quality**. Howard University Leadership Academy

1998 **Problem-Based Learning**. Southern Illinois University School of Medicine.

1999 **Faculty Workshop on Educational Technology**. Office of the Provost, Howard University, Founders Library, April 3, 1999.

1999 **Teaching Students to Enter, Analyze, and Evaluate Points of View.** Workshop held by the Foundation for Critical Thinking. Seattle, Washington. April 24-25, 1999.

1999 **Writing Across the Curriculum** Faculty Workshop. Writing Center, Locke 100, Howard University, June 1-2, 1999.

2001 **History of Howard University**. Howard University Leadership Academy, 8 June 2001.

2001 **Animal Models of Breast Cancer**. Workshop sponsored by Howard University College of Medicine/HU Cancer Center and Walter Reed Army Institute of Research. 19 June 2001.

2001 **Current Topics in Genome Research**, National Human Genome Research Institute, NIH, August 6 - 9, 2001. (Ref. Jeff Witherly, Office of Science Education, NHGRI, E-mail: jlw@nhgri.nih.gov).

2003 **Free Radicals: The Pros and Cons of Antioxidants**, Masur Auditorium, NIH, Bethesda, MD. June 26-27, 2003.

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Bremner, T., Kidd, L. C., Kim, K. S., Groupman, J. D., and Ashktorab, H. (2000). Influence of *Helicobacter pylori* on reactive oxygen-induced gastric epithelial cell injury. *Carcinogenesis* **21**, 2091-2095.

GRANTS/AWARDS

1980-1983: Bremner, T. A. Mitochondrial Involvement in Plant Tumor Induction. MinorityBiomedical Research Support Program, Division of Research Resources, NIH.

1983-1986: Bremner, T. A. Mitochondrial Involvement in Retroviral Oncogenesis.

1987: Bremner, T. A. Active oxygen regulation of differentiated functions in cultured rat hepatoma cells. Howard University Faculty Research Support Grant.

1995-1998 Bremner, T. A. (Co-PI), Howard University). Tsan, M.-F. (Co-PI, Stratton Medical Center, Albany, NY), Oxidant, antioxidant enzyme and leukemic cell differentiation. Department of Veterans Affairs Medical Research Service, Veterans Administration. S. Stratton Medical Center, Albany, NY 12208. (Howard), (Stratton VA). 10/1/1995 - 9/30/1998. (funded).

1998: Howard University Faculty Merit Award (December 1998)

1999 Academic Excellence Award (Lucile L. Adams-Campbell and T. A. Bremner, Co-PIs. Establishment of a Graduate Oncology Course.

1999: Howard University Faculty Merit Award **(December 1999)**

2000 Howard University Faculty Merit Award (December 2000)

2000: U.S. Army Medical Research and Materiel Command. Award Category: Institutional Training Grant. **A Training Program in Breast Cancer Research Using NMR Techniques. Paul C. Wang, Ph.D., (PI).** Scientific Participants and mentors: **Paul C. Wang, Ph.D.,** (Medical Physics/Radiology); Verle E. Headings, M.D., Ph.D., (Genetics); **Theodore A. Bremner, Ph.D.**, (Biology); Lucile L. Adams-Campbell, Ph.D., (Epidemiology); Eva J. Duckett, M.D., (Radiology); Mohamed F. Chouikha, Ph.D., (Electrical Engineering); Rajagopalan Sridhar, Ph.D., (Radiation Therapy); 7/01/00 - 6/30/04. Roles in project: (1) To serve as a graduate research mentor; (2) to develop, test, and implement a cell biology training module for engineering graduate students to prepare them for participation in cancer research seminars and the proposed graduate oncology course.

2001: NIH/NCI, #1U54CA91431-01. **Howard-Hopkins Cancer Partnership.** (Lucile L. Adams-Campbell, Ph.D., PI), 5/01/01 - 4/30/06.
Project: **Cancer Education Program**; Theodore A. Bremner, Ph.D. (Howard University Cancer Center) and Donald Coffey, Ph.D. (Johns Hopkins Oncology Center), co-principal investigators. **Course Director:** Theodore A. Bremner. **Support:** 100% effort (summer); 20% effort (academic year). (5/01/01 - 4/30/03).

2001 **Distinguished Faculty Author Award**, Howard University, 17 April 2001.

2001 **Award in recognition of excellence in science and education**, National Human Genome Research Institute, NIH, Bethesda, MD. 9 July 2001. (Ref. Jeff Witherly, Office of Science Education, NHGRI, E-mail: jlw@nhgri.nih.gov).

2001 Howard University Faculty Merit Award (Dec 2001).

2002 U.S Army Medical Research Acquisition Activity. Award No: DAMD17-02-1-0408. Theodore. Bremner, (P.I.). **"Anti-estrogen Regulation of Macrophage Products That Influence Breast Cancer Cell Proliferation and Susceptibility to Apoptosis."** (2002-2005).

2005 Department of Defense, Breast Cancer Research Program, Paul Wang (PI), A Partnership Training Program in Breast Cancer Research . Theodore A. Bremner, Co-investigator and PI of sub-project 2 "Imaging the Effects of Macrophage function on Tumor Promotion." (7/1/2005 – 6/30/2009).

investigator and PI of sub-project 2 "Imaging the Effects of Macrophage function on Tumor Promotion." (7/1/2005 – 6/30/2009).

INVITED RESEARCH SEMINARS

1982: Coordinate Regulation of Superoxide Dismutase and Peroxidase in Normal and Transformed Tissues of *Nicotiana tabacum*. Beltsville Agricultural Research Center, 15 October 1982.

1983: Superoxide Dismutase. Symposium on "Genetics of Susceptibility and Resistance to Infections, Inflammatory and Neoplastic Diseases". Litton Bionetics, Inc., Kensington, MD, 30 September 1983.

1984: Regulation of Superoxide Dismutase Gene Expression in Normal and Transformed NIH Swiss/3T3 Cells. American Type Culture Collection. Rockville, MD, 24 August 1984.

1987: Oxyradicals: Their Role in Cellular Differentiation and Neoplasia. Department of Biochemistry, College of Medicine, Howard University, 24 September 1987.

1988: Regulation of active oxygen-scavenging enzymes during PMA-induced differentiation of human promonocytic leukemia (THP-1) cells. Department of Biology, Bethune-Cookman College, Daytonna Beach, Florida, 11 November 1988.

1993: Redox regulation of differentiation in THP-1 promonocytic leukemia cells. Microbiology Research Seminar, Department of Microbiology, Howard University College of Medicine, 334 S. G. Mudd Building, 8 January 1993.

1996 Reactive oxygen species and antioxidant enzymes in differentiating THP-1 promonocytic leukemia cells. Neuroscience Research Seminar Series, Department of Physiology and Biophysics, College of Medicine, Howard University, Rm. 200 S.G. Mudd Building, 23 April 1996.

1997 Differentiation of promonocytic Leukemia Cells: A long march with many stops. Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University, Eddy Auditorium, BMC, 21 February 1997.

1997 Redox modulation of cellular functions in differentiation and neoplasia: Glucose-6-phosphate dehydrogenase and differentiation of THP-1 promonocytic leukemia cells. Research Seminar, Department of Biology, The Catholic University of America, Washington, DC. 20 October 1997. (Ref.: Dr. Lorette Javois, Dept. of Biology, CUA).

1997 "Fas-Mediated apoptosis and cytotoxicity of cancer cells: observations on promonocytic leukemia." Basic Research Division, Howard University Cancer Center, Thursday 4 December 1997, 12:00 noon, Rm 201 Cancer Center.

1998 "Cytotoxicity of promonocytic leukemia cells and their escape from Fas-mediated apoptosis." Seminar, Department of Anatomy, College of Medicine, Howard University, Wednesday 14 January 1998, 12:00 noon Rm 1301 S.G. Mudd Building.

1999-2003 "Cancer". Invited lectures given to the graduate cell biology course in the Department of Microbiology. Dr. Morris Hawkins, Jr., coordinator, 202-806-4321

PARTICIPATION IN SCIENTIFIC MEETINGS

1971: Bremner, T. A. Tissue distribution and function of octanol dehydrogenase in *Drosophila metzii*. Genetics Society of America, Rochester, NY.

1971: Bremner, T. A. Tissue distribution and regulation of octanol dehydrogenase isozymes in *Drosophila metzii* and *D. pellewae*. Isozyme Conference, St Thomas, U.S. Virgin Islands, December 1971.

1973: Collins, M. S., and Bremner, T. A. Isozyme variants of selected castes and species of termites. Entomological Society of America, Dallas, TX, November 1973.

1976: Rosenspire, A., Bremner, T. A., and Pogell, B. M. Expression of differentiated function in cultures of isolated sea-urchin micromeres. Marine Biological Laboratory Conference, Woods Hole, MA August 1976.

1979: Chairman, Symposium on "Biology, culture and human evolution." Annual Meeting of the American Association for the Advancement of Science, Houston, TX, January 1979.

1983: Chairman, Cell Biology Session, 11th Annual MBRS Symposium, Washington, DC, April 1983.

1983: Whiteside, C., Blackmon, R. H., and Bremner, T. A. 1983. Superoxide dismutase regulation in normal rat mammary tissues and DMBA-induced mammary tumors. Isozyme Conference, Frenchman's Reef, U.S. Virgin Islands, December 1983. Paper presented by CW.

1984: Chairman, Developmental Biology Session, 12th Annual MBRS Symposium, Washington DC, April 10-13, 1984.

1984: Bremner, T. A., and Whiteside, C. A novel cyanide-resistant superoxide dismutase associated with microsomal fractions of mouse liver. Seventh Annual Symposium of Biology for Consortium Universities of Metropolitan Washington, George Mason University, March 2, 1984.

1984: Soodeen, C. J. and Bremner, T. A. Catalytic and structural heterogeneity of purine nucleoside phosphorylase-1A variants among subspecies of *Mus musculus*. Seventh Annual Symposium of Biology for Consortium Universities of Metropolitan Washington, George Mason University, March 2, 1984. Paper presented by CJS.

1984: Soodeen, C. J. and Bremner, T. A. Catalytic and structural heterogeneity of purine nucleoside phosphorylase-1A variants among subspecies of *Mus musculus*. 41st Joint Annual Meeting of the National Institute of Science, Beta Kappa Chi Scientific Honor Society and the Brookhaven Semester Program. Atlanta, GA, March 28-31, 1984. Paper presented by CJS.

1984: Whiteside, C., and Bremner, T. A. A cyanide-insensitive superoxide dismutase associated with mouse liver microsomes. 41st Annual Meeting NIS/BKX/BSP, Atlanta, GA, March 28-31, 1984. Paper presented by CW.

1984: Soodeen, C. J. and Bremner, T. A. Catalytic and structural heterogeneity of purine nucleoside phosphorylase-1A variants among subspecies of *Mus musculus*. Sixth Annual Graduate Student Research Day, Howard University, April 18, 1984. Paper presented by CJS.

1984: Blackmon, R. H., and Bremner, T. A. Regulation of LDH A and B genes in transformed murine cells. Sixth Annual Graduate Student Research Day, Howard University, April 18, 1984. Paper presented by RB; **won first prize in biology competition.**

1986: Holden L. M., and Bremner, T. A. Thermotolerance and free radical metabolism in *Crithidia luciliae luciliae* and *C. l. thermophila*. Joint Annual Meeting of the National Institute of Science, Beta Kappa Chi Scientific Honor Society and the Brookhaven Semester Program, Norfolk, VA, March 26-29, 1986. Paper presented by LMH.

1986: Asseffa, A., and Bremner, T. A. Induction of superoxide dismutase activity during differentiation of human promonocytic leukemia cells treated with tetradecanoylphorbol acetate. NIS/BKX/BSP Meeting, Norfolk, VA, March 26-29, 1986. Paper presented by AA.

1986: Asseffa, A. and Bremner, T. A. Induction of superoxide dismutase activity during differentiation of human promonocytic leukemia cells treated with tetradecanoylphorbol acetate. Ninth Symposium of Biology for Consortium Universities, Georgetown University, Washington, DC, April 11, 1986. Paper presented by AA.

1993: Jack, M., Earlington, M., Williams, T., Bremner, T., Asseffa, A., and Smoot, D. Exposure of *Helicobacter pylori* to differentiated THP-1 cells. Association of Academic Minority Physicians.

1993: Dickson, L.A., Asseffa, A., Mohla, S., & **Bremner, T.A.** Phorbol Myristate Acetate-Differentiated THP-1 Cells Are Functional Macrophages. (Abstract #272). *FASEB J. 7:* (#7), A1099. Poster at the American Society for Biochemistry & Molecular Biology --Division of Biological Chemistry-American Chemical Society Joint Meeting, San Diego, CA, 5/30/93 - 6/3/93.

1993: Asseffa, A., Dickson, L. A., Tuncali, T., Smoot, D. T., and **Bremner, T. A.** Retinoic acid inhibits proliferation and increases MHC class I mRNA in HT-29 colon carcinoma cells. 46th Annual Symposium on Fundamental Cancer Research, The University of Texas M. D. Anderson Cancer Center, J. W. Marriott Hotel, Houston, Texas, October 12-15, 1993.

1993: **Bremner, T. A.**, and Asseffa, A. (1993). Tamoxifen inhibits phorbol ester-induced differentiation of THP-1 myeloid leukemia cells. 46th Annual Symposium on Fundamental Cancer Research, The University of Texas M. D. Anderson Cancer Center, J. W. Marriott Hotel, Houston, Texas, October 12-15, 1993.

1994: **Bremner, T. A.**, D'Costa, N., Dickson, L. A., and Asseffa, A. A Decrease in Glucose 6-Phosphate Dehydrogenase Activity and mRNA is an Early Event in Phorbol Ester-Induced Differentiation of THP-1 Promonocytic Leukemia Cells. (Abstract #939, 12:15 - 2:00 pm, 05/24/94). FASEB J. 8 (#7): A1420 Abstract #939 (1994). Poster presentation at the American Society for Biochemistry & Molecular Biology, Washington Convention Center Exhibition Hall, Washington, DC 5/21-25/94.

1995: **Bremner, T. A.** Tamoxifen inhibits phorbol ester-induced differentiation of THP-1 myeloid leukemia cells. Howard University Cancer Center Research Symposium on Cancer Etiology and Treatment. Ambulatory Care Center Auditorium, November 17, 1995.

1997 Chatterjee, D., Han, Z., **Bremner, T.A.**, and Wyche, J.H. Differentiation of human myeloid leukemia cells results in the induction and mitochondrial localization of Bak and enhances susceptibility to apoptosis. 37th American Society for Cell Biology Annual Meeting, Dec. 13 - 17, 1997, Washington, DC. (*Mol. Biol. Cell* ***8***, 33a, Supplement)

1999 Maheshwari, J. G., White, J. E., Bremner, T. A., Sacco, J., and Tsan, M. -F. Resveratrol induces Fas signaling-independent apoptosis in THP-1 human monocytic leukemia cells. American Society for Hematology Annual Meeting, New Orleans, LA, Dec. 3 - 7, 1999.

2003 Attended: AACR 2003 Annual Meeting (postponed from Toronto) Washington Convention Center, Thursday 10 July – Monday 14 July 2003.

2003 Morris, G. S. and Bremner, T. A. Tamoxifen alters the inflammatory cytokine transcriptional profile induced in THP-1 macrophages by MCF-7 breast cancer cells. AACR-NCI-EORTC International Conference on *Molecular Targets and Cancer Therapeutics*. Hynes Center, Boston, MA, November 17 – 21, 2003. Abstract published in the Conference Proceedings as a supplement to the November 15, 2003 issue of *Clinical Cancer Research*.

2004 Morris, G. S., Henry, G. A., and Bremner, T. A. THP-1 macrophages stimulate proliferation, protect against tamoxifen killing, and modulate angiogenesis-related gene expression in MCF-7 breast cancer cells. Annual Meeting of the American Association for Cancer Research, Orlando, FL (Abstract 5201).

2004 Jin, Z., Morris, G. S., and Bremner, T. A. Reciprocal regulation of angiogenesis-related gene expression in co-cultured MCF-7 breast cancer cells and THP-1-derived macrophages. 44th Annual Meeting of the American Society for Cell Biology, Washington, DC, 4 – 8 December, 2004. (Abstract L186).

TRAINING

Post-doctoral:

Zhe Jin, M.D., Ph.D. (2004 – 2005).

Graduate (M.S.):

Yvonne A. Reid, M.S. (botany/microbiology).
D. K. Joshi, M. S. (botany/microbiology).
Eric Thompson, M.S. (botany/microbiology).
Carolyn Bowman, M.S. (botany/microbiology).
Ronald Blackmon, M.S. (zoology; biochemical genetics) 1984 (MARC Fellow).
Angela Martin Tishavakunda (M.S., biology1994)
Dana N, Jones (M.S., biology, 1999.
Theodore O. Garnett, (M.S., biology, 2000)

Graduate (Ph.D.):
Catherine Whiteside, Ph.D. (zoology; biochemical genetics) 1984 (MARC Fellow).
Claudia J. Soodeen, Ph.D. (zoology, biochemical genetics) 1986 (MARC Fellow).
Amha Asseffa, Ph.D. (zoology; biochemical genetics) 1987.
Ronald H. Blackmon, Ph.D. (zoology; biochemical genetics) 1988.
Marilyn A. Emtage, Ph.D. (zoology; biochemical genetics) 23 July 1991.
Gay S. Morris, (expected date of graduation May 2004).

DEPARTMENTAL COMMITTEES

Chairman, Curriculum Committee, Department of Zoology, 1984-1986
Member, Scholarship Committee, Department of Zoology
Member, *Ad Hoc* Committee to evaluate the zoology graduate program, 1985
Chairman, Curatorial Committee, Department of Zoology, 1984-1986
Member, Graduate Studies Committee, Department of Zoology, 1985-1987
Member, Senior Comprehensive Committee, Department of Zoology, 1984-1987
Undergraduate Research Coordinator, Zoology, 1991-1992
Member, Executive Committee, Department of Biology, 1992-1993.
Member, Executive Committee, Department of Biology, 1993-1994.
Member, Executive Committee, Department of Biology, 1994-1995.
Chairman, Curriculum Committee, Department of Biology, 1995-1996.
Member, Safety Committee, Department of Biology, 1995-1996.
Member and Chair, Graduate Curriculum Committee, Department of Biology, 1998-1999.
Member, Graduate Admissions Committee, Department of Biology, 1999-2000.

UNIVERSITY COMMITTEES

Member, Internal Quality Control Committee for Project One, Nutritional Status and the Outcome of Pregnancy, of the Program Project, "Nutrition, Other Factors, and the Outcome of Pregnancy." (Dr. Cecile H. Edwards, Dean, School of Human Ecology, Project Director) 1985.
Member, examination committee for the final oral examination in defense of the thesis of Miss. Allyson Stanley Ambrose, Master's degree candidate in the Department of Zoology, 24 May 1985.
Member, examination committee for the final oral examination in defense of the dissertation of Miss. Elaine V. Knight, doctoral candidate in Human Ecology, 25 March 1986.
Member and major advisor, examination committee for the final oral examination in defense of the dissertation of Miss. Claudia J. Soodeen, doctoral candidate in the Department of Zoology, 26 March 1986.
Member, examination committee for the final oral examination in defense of the dissertation of Mr. Gary L Harmon, doctoral candidate in the Department of Zoology, 1 December 1986
Member, Advisory and Review Committee for the Deanship of the College of Liberal Arts (Search Committee), 1986-1987.
Member, examination committee for the final oral examination in defense of the dissertation of Mr. Albert M. Stoddart, doctoral candidate in Human Nutrition and Food, School of Human Ecology, March 27, 1987.
Member and major advisor, examination committee for the final oral examination in defense of the dissertation of Mr. Amha J. Asseffa, doctoral candidate in the Department of Zoology, July 13, 1987.
Chairman, Administrative Review Committee to evaluate the graduate program in the Department of Political Science, (Esther Ottley, Acting Dean, Graduate School of Arts and Sciences) December 1987.
Member and major advisor, examination committee for the final oral examination in defense of the dissertation of Mr. Ronald H. Blackmon, doctoral candidate in the Department of Zoology, 11 February 1988.

Member and major advisor, examination committee for the final oral examination in defense of the dissertation of Miss. Marilyn E. Emtage, doctoral candidate in the Department of Zoology, July 1991.
Member, Advisory Committee on the Afro-American Studies Course, 1987.
Member, examination committee for the final oral examination in defense of the dissertation of Mr. Mohammad Ashraf, doctoral candidate in the Department of Zoology, 24 March 1988.
Member, Curriculum Commission College of Liberal Arts, 1987-1990.
Chairman, Search Committee for Chairperson of the Department of Biology, 1991.
Member, Search Committee for Chairperson of the Department of Biology, 1992.
Member, The Honors Council, College of Arts and Sciences, 1990 - 1992.
Member, Admissions Committee, College of Arts and Sciences, 1988-1990.
Member, Committee on Academic Status, College of Arts and Sciences, 1990 - 1992.
Member, Handbook Committee, Faculty Senate, 1994-1995; 1995-1996.
Member (at-large), Council of the Faculty Senate, 1994-1997.
Member, Honors Program Advisory Board, College of Arts and Sciences (Appointed by the Dean of the College), November 1994 -.
Member, Steering Committee, Council of the Faculty Senate, 1995-1996.
Member, Alumni Awards Committee, College of Arts and Sciences, 1995-1996.
Member, (elected) Executive Committee, Howard University Cancer Center, 1995-present.
Member (and mentor), examination committee for the defense of the master's thesis of Ms. Dana N. Jones, M.S. candidate in the Department of Biology, 4 Nov 1999.
Member, Honors Council Scholarship Committee, College of Arts and Sciences, 1995-1996.
Member, Honors Council, College of Arts and Sciences, 1999-2000, 2000-2001.
Member, Appointment and Promotions Committee, Graduate School of Arts and Sciences,1999-2000, 2000-2001, 2001-2002.
Alternate representative of the Graduate School of Arts and Sciences to the Faculty Senate, 1998-2000; 2000-2001
Member, Steering Committee of the Faculty Senate, 2000-2001.
Co-chair, Faculty Senate Retreat, School of Law, Nov. 4, 2000.
Chairman, Ph.D. examination committee for Ms. Eba Ongele, doctoral candidate in the Department of Biology, 27 March 2000.
Member, M.S examination committee for Ms. Marianna Siewe, M.S. candidate in the Department of Biology, 27 June 2000.
Member (and mentor), M.S. examination committee for Mr. Theodore O. Garnett, M.S. candidate in the Department of Biology, 19 July 2000.
Vice chairman, Natural Sciences Division, College of Arts and Sciences, Howard University (2003 – 2005).
Chairman, Natural Sciences Division, College of Arts and Sciences, Howard University (2005 – 2007).
Chairman, Retreat Committee, Howard University Faculty Senate (2005).
Chairman (elect), Howard University Faculty Senate (Term August 1, 2005 – June 30, 2007)

REVIEWS/SITE VISITS/STUDY SECTIONS

1981 Member, Site Visitation Team, California State University at Fresno, September 1981.
1983 Reviewed grant proposal for the Division of Research Resources, NIH, 1983.
1983 Reviewed manuscript for *Biochemical Genetics* (1983).
1984 Reviewed proposal for Howard University Research and Development Grant Program, 1984.
1994 Reviewer for *Biology* (3rd Ed) by Neil A. Campbell (for 4th Ed.). The Benjamin/Cummings Publishing Company, Inc. Tabinda N Khan, Editorial Assistant, Life Sciences.
1998 Panelist, NSF Graduate Research Fellowship Program (Feb. 12 - 14, 1998)

1998 U.S. Army Medical Research and Materiel Command, 1998 Breast Cancer Research Program (BCRP) **Scientific Peer Review, Panel: Cell Biology # 1,** Sheraton Norfolk Waterside Hotel, Norfolk, VA, September 23-25, 1998.

1999 Panelist, **NSF Graduate Research Fellowship Program**, Hyatt Regency Hotel, Crystal City, VA. Feb 4 to 7, 1999.

1999 U.S. Army Medical Research and Materiel Command, 1999 Breast Cancer Research Program (BCRP) **Scientific Peer Review, Panel: Cell Biology # 1**, Sheraton Premiere Hotel, Tyson's Corner, Vienna VA, August 29-31, 1999.

2000 Panelist, NSF Graduate Research Fellowship Program, Doubletree Hotel, Arlington, VA, Feb. 17 - 19, 2000.

2000 Reviewed manuscript for *Cancer Letters*. (Letter of request from Frederick A. Beland, Ph.D., editor. Tel.: (870) 543-7202. E-mail: fbeland@nctr.fda.gov).

2001 Reviewed manuscript for *Journal of Bone and Mineral Research.* (Letter of request (8/7/2001) from John Eisman, M.B.B.S., M.D., Associate Editor. Editorial Office Tel.: (919) 620-0681; E-mail: journal@jbmr.org).

2002, 2003: Member, Training Grant Advisory Committee ("Laboratory Research Training in Pediatric Oncology-Hematology" grant), Sidney Kimmel Comprehensive Cancer at Johns Hopkins. Committee evaluates and selects candidates for post-doctoral fellowships.

2004 Scientific Reviewer, Tumor Biology I Study Section. Susan G. Komen Breast Cancer Foundation, Inc. (Ref. Deborah L. Price, MHA, Grant Review Specialist, 5005 LBJ Freeway, Suite 250, Dallas, TX 75244; 972-855-1640).

2004 Scientific Reviewer, Department of Defense Ovarian Cancer Research Program, April 21 – 23, 2004, Landsdowne, VA. (Contact: Glacia Townsend)

2004 Panelist, Loan Repayment Program, NCMHD, NIH 16 – 18 May, 2004, Bethesda, MD. (Contact: Lorrita P. Watson).

2004 Panelist, Infectious Diseases Training Grant Study Section, Centers for Disease Control and Prevention, August 9 – 13, 2004, Atlanta, GA.

2005 Panelist, Loan Repayment Program, NCMHD, NIH, 4 April 2005 (Contact: Lorrita P. Watson).

2005 Scientific Reviewer, Prostate Cancer Research Program, USAMRMC, CDMRP, Department of Defense, 7 – 9 April 2005, Tyson's Corner, VA (Contact: Charles H. Rodgers).

COMMUNITY SERVICE

Judge, Afro-Academic Cultural Technological and Scientific and Cultural Olympics (ACTSO), Banneker High School, Washington, DC, 26 April 1986.

Coordinator (and Instructor), 1987 Basic Cell and tissue Culture Course, sponsored jointly by the National Capital Area Tissue Culture Society (NCATCS) and the Department of Microbiology, The George Washington University Medical Center, 3-10 June 1987, Ross Hall, GWU, Washington, DC. The course was taught by seventeen instructors from eleven universities and research institutions in the Washington and Baltimore metropolitan areas.

Coordinator, Mini-Workshop on plant tissue culture sponsored jointly by the NCATCS and the Beltsville Agricultural Research Center (BARC), held at BARC, 27-29 March 1987

Course Coordinator (and Instructor) for "Workshop on Basic Cell Culture and Cytochemical Techniques". Mary Washington College, Fredericksburg, VA, sponsored by the NCATCS. 20-22 November 1987.

Judge ACTSO, Dunbar High School, Washington, DC, 25 April 1987.

Instructor, 1988 Basic Cell and Tissue Culture Course, sponsored jointly by NATCS and the Department of Biology, University of Maryland, Baltimore Campus. June 1988.

Judge, Oxon Hill High School Science Fair (Biochemistry), 7 March 1987, & March 1988.

Attended Department of Energy-sponsored "Science and Engineering Research Semester (SERS)" Conference, Argonne National Laboratory, April 1988.

Prepared questions for the new Graduate Record Examination Biochemistry, Cell and Molecular Biology Test, 1989.

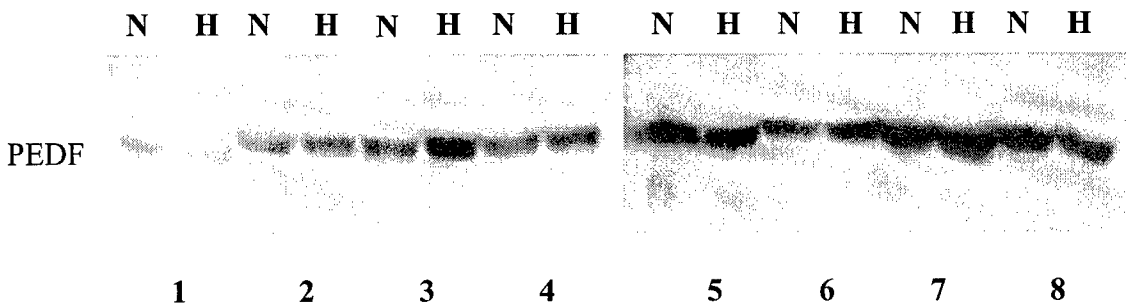
Reviewed Chapter 41 from the third edition of Campbell's ***Biology*** (November 1994). Ref: Tabinda N. Khan, Editorial Assistant, Life Sciences, The Benjamin/Cummings Publishing Company, Inc. (1-800-950-2665 x 887). Listed among reviewers of the 4th edition.

Delivered a plenary Lecture "**Molecular strategies for vector control**" at the 9th Annual Meeting of the Ethiopian Veterinary Association, Ministry of Natural Resources Development and Environmental Protection, Addis Ababa, Ethiopia.

Conducted a three-day workshop on **Biochemical Techniques for the Biomedical and Agricultural Sciences**, at the National Animal Health Research Centre at Sabeta, Ethiopia. Workshop sponsored jointly by: the National Animal Health Research Centre at Sabeta; the [Ethiopian] Ministry of Agriculture; Ethiopian Science and Technology Commission; The Permaculture and Parasitology Institute (at Kebena), and the International Centre of Insect Physiology and Ecology (ICIPE)- Ethiopia Project. July 11 to July 13, 1995.

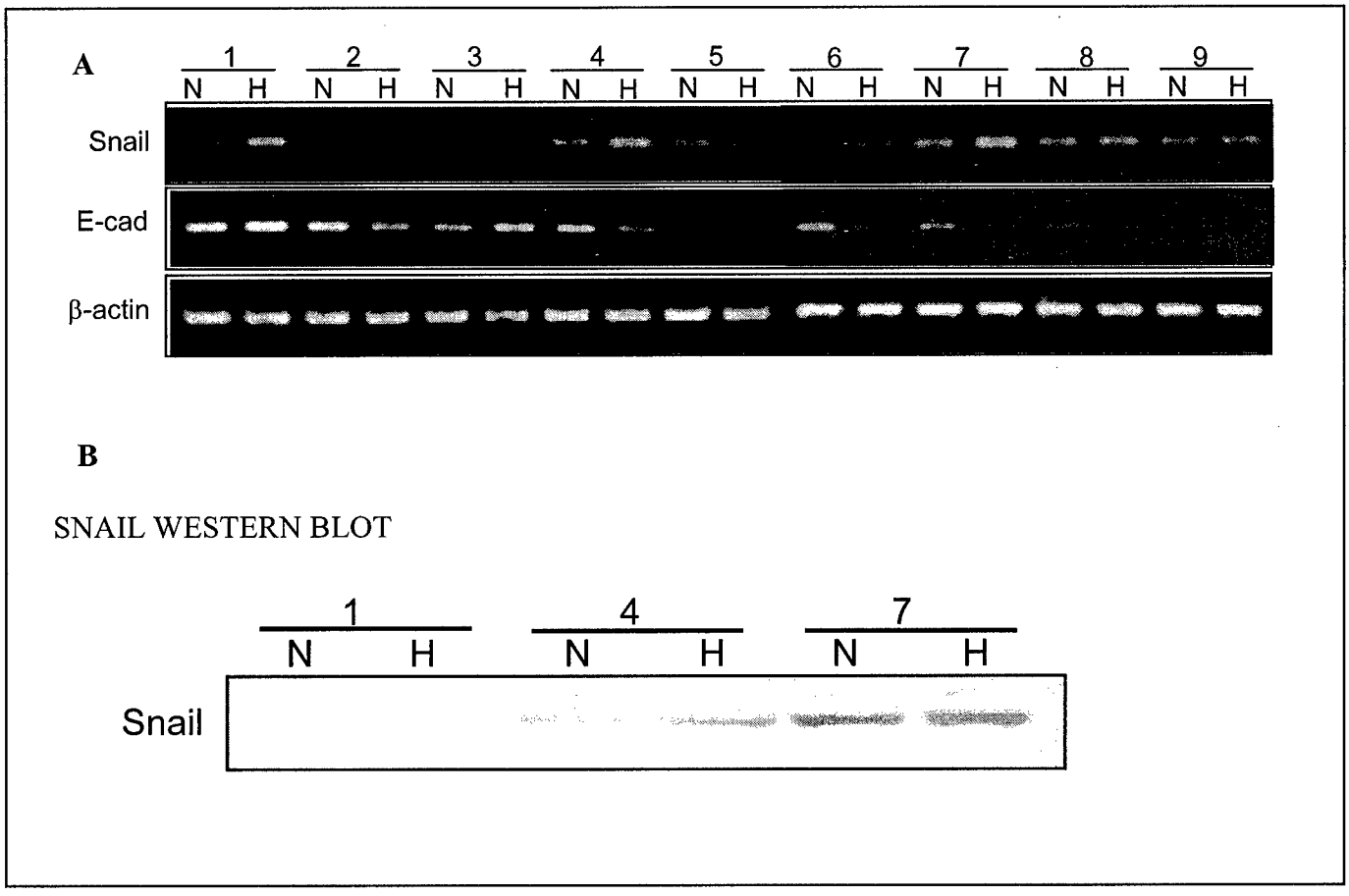
Conducted a two-day workshop on **Biochemical Techniques for the Biomedical Sciences** at the Ethiopian Health and Nutrition Research Institute (EHNRI), Addis Ababa, Ethiopia. Sponsored jointly by: The Permaculture and Parasitology Institute (Capacity-Building Program in the Agricultural and Biomedical Sciences), the Ethiopian Health and Nutrition Research Institute (EHNRI), and the Ethiopian Science and Technology Commission. August 1 and 2, 1995.

SUPPORTING DATA



Western blot of PEDF. MCF-7 cells were grown alone or in co-culture with THP-1 macrophages, under various conditions. N = normoxia, H = hypoxia. Where cells are co-cultured, the RNA was obtained from the cell type in bold font: 1, MCF-7 ; 2, MCF-7 + tamoxifen (30 μM) ; 3, **MCF-7** + Macrophages ; 4, (**MCF-7** + Macrophages) + tamoxifen; 5, Macrophages ; 6, Macrophages + tamoxifen ; 7, MCF-7 + **Macrophages**; 8, MCF-7 + **Macrophages**) + tamoxifen.

SNAIL AND E-CADHERIN mRNA



A, RT-PCR analysis of Snail, E-cadherin and beta-actin in MCF-7 cells. **B**, Western blot of Snail in MCF-7 cells. N=normoxia, H= hypoxia, 1=MCF-7, 2=MCF-7+Tamoxifen,3=MCF-7+Faslodex, 4=MCF-7+macro, 5=(MCF-7+macro)+Tamoxifen, 6=(MCF-7+macro)+Faslodex, 7=MCF-7+activated macro, 8=(MCF-7+activated macro)+Tamoxifen, 9=(MCF-7+activated macro)+Faslodex. P=positive control, M=methylation-specific products, UM, nonmethylation-specific products.